2. Synopsis

Brief Final Study Report: Study H3E-ES-S085

Title of Study: Phase I/II study of bi-weekly ALIMTA plus cisplatin in patients with non-resectable locally advanced or metastatic urothelial cancer

Investigator/s: 7 principal investigators participated in this multicenter study: [redacted].

Study Center/s: This study was carried out in the 7 Spanish centers above mentioned.

Publication/s based on this study: *"Phase I study of bi-weekly pemetrexed (P) plus cisplatin (C) in patients with advanced cancer".*

Length of Study: 21 months. Planned first enrolled subject: 08 August 2006. Planned last subject visit: 12 May 2008.	**Phase of Development:** I/II

Objectives:

Primary Objective:

Phase I

- To determine the maximum tolerated dose of bi-weekly ALIMTA plus cisplatin in patients with non-resectable locally advanced or metastatic urothelial cancer with no curative or palliative standard treatment options.

Phase II

- To assess the antitumor activity of bi-weekly ALIMTA plus cisplatin in chemonaïve patients with locally advanced (non-resectable) or metastatic urothelial cancer, as assessed by response rate (proportion of patients with complete or partial response).

Secondary objectives

Phase I

- To determine the toxicity of the chemotherapy combination in this patient population, both quantitatively and qualitatively.
- To determine the recommended dose of bi-weekly ALIMTA plus cisplatin for the phase II study.
- To document the antitumor activity of the bi-weekly ALIMTA plus cisplatin combination in patients with measurable disease.

Phase II

- To assess the toxicity profile of the chemotherapy combination in patients with urothelial cancer.
- To assess the following time-to-event variables:
  - Time to response.
  - Duration of the response.
  - Duration of stable disease.
  - Time to documented disease progression.
  - Time to treatment failure.
  - Progression-free survival.
  - Overall survival.

Study Design: This study comprises 2 consecutive phases: phase I, open, dose-finding study, with bi-weekly administration of ALIMTA, followed by a phase II, multicenter, non randomized, open study, using the dose determined in the phase I study, in chemonaïve patients with locally advanced or metastatic

urothelial cancer.

Number of patients:

Planned: 33 patients for phase I study.

Entered: 38 patients.

Protocol completed: 2 patients.

Diagnosis and Main Criteria for Inclusion:

Phase I: Patients > 18 years old, with histologic or cytologic diagnosis of locally advanced or metastatic cancer (both measurable and non-measurable disease), with no potentially curative standard treatment option, ECOG performance status of 0 or 1 and an estimated life expectancy of at least 12 weeks; who have adequate organ function and have not received prior radiation to the whole pelvis, although prior palliative radiotherapy is permitted if discontinued 2 weeks prior to study inclusion.

Phase II: Patients > 18 years old, with histologically confirmed transitional cell carcinoma of the urothelium (locally advanced [Stage IV, according to UICC TNM classification] and measurable disease [according to RECIST criteria]) and ECOG performance status of 0, 1 or 2, a life expectancy of at least 12 weeks and an adequate organ function, as assessed by laboratory tests.

For both phases, females of child bearing potential must use reliable contraception methods and have a negative pregnancy test.

Test Product, Dosage and Mode of Administration:

- ALIMTA: Initial dose of 300 mg/m^2. Dose will be escalated until maximum tolerated dose is reached (intravenously administered).
- Cisplatin: 50 mg/m^2, intravenously administered.

Duration of treatment:

Phase I: dose-finding study of bi-weekly administration of cisplatin (50 mg/m^2) plus ALIMTA (increasing doses, initial dose of 300 mg/m^2). Infusions will be administered on days 1 and 15 of each 28-day cycle.

Phase II: bi-weekly cisplatin (50 mg/m^2) plus ALIMTA (recommended phase II dose, determined in the phase I study), administered on days 1 and 15 of each 28-day cycle.

Reference Therapy, Dose and Mode of Administration: N/A.

Variables:

Efficacy:

- Study response rate.
- Time-to-response.
- Duration of complete or partial response.
- Duration of stable disease.
- Time to documented disease progression.
- Time to treatment failure.
- Progression-free survival.
- Overall survival.

Safety:

- Adverse Events.
- Toxicities.
- Laboratory data.
- Physical exam and performance status.
- Drug exposure time.

Method:

Statistics:

For phase I study, it was estimated that sample size would include up to 24 patients. For phase II study, with the aim of having 33 evaluable patients for efficacy, 18 patients would be enrolled during the first phase, while 15 patients would be enrolled during the second phase. Assuming the "true" response

probability was 20%, the probability that the study ended during the first phase would be 71,64%. However, if the "true" response probability was 40%, the probability of an early discontinuation of the study during the first phase would be 9,42%. Alpha level was 0.05 and the study was provided with a power of 80%. If up to 4 responses were observed during the first phase of the study, this would cause the early study discontinuation. If up to 10 responses were observed at the end of the trial, it would not be worthwhile to continue with the drug research.

All efficacy analyses included the intention-to-treat population.

The primary efficacy endpoint (response rate during the study) was presented by each cycle and the 95% confidence intervals for CR, PR, SD and PD (respectively) were calculated using SAS "Proc freq" procedure.

All secondary variables were analyzed using the Kaplan-Meier method and SAS "Proc lifetest" procedure. Survival was censored at the date of the last visit for patients who were still alive at that time. Additionally, duration of CR or PR, duration of SD and time to documented disease progression were analyzed, excluding those patients who had started a postdiscontinuation treatment before initial documentation of progression.

With regard to safety variables, adverse events were coded according to MedDRA dictionary, version 9.0.Toxicities were assessed by cycle and patient, reporting the worst grade for each cycle and the worst grade per patient, respectively. Laboratory data, weight changes during the study and the different assessments of ECOG performance status within a cycle were described. Additionally, drug exposure time was presented.

Summary:

After completion of the phase I clinical trial, it was considered that 800 mg/m^2 and 100 mg/m^2 were the appropriate ALIMTA and cisplatin doses (respectively) to be further investigated in the phase II clinical study. ALIMTA dose intensity was 172.8 mg/m^2/week, with 95% confidence interval ranging from 172.8 to 181.1. Final cisplatin dose was 22.3 mg/m^2/week (95% CI 84.6 ; 94.7).

Results described in this report are based on the phase II clinical trial.

In this study a total of 38 patients were included. Treated patients' mean age was 67.1 years old (SD 8.7). Of all patients, 81.6% were males. The mean time to diagnosis was 1 year (SD 1.4). 84.2% of the patients had localized bladder cancer, and 78.2% of the patients had metastatic disease. 86.8% of the patients had normal physical examination results, and 94.7% of the patients had an ECOG performance status of 0 or 1 at the study inclusion. 94.7% of the patients had not previously received either systemic treatments or curative radiotherapy. 94.7% of the patients had prior surgery.

The primary objective of this study phase was to assess the antitumor activity of the bi-weekly ALIMTA plus cisplatin combination, as assessed by the response rate (proportion of patients achieving complete or partial response). Of the 38 patients entered in this study phase, 15 patients (39.5% [95% CI 24.04%; 56.6%]) had a best study response of complete or partial response.

The secondary variable results were as follows:

- Median time to complete or partial response was 128 days (mean: 111.816; standard error: 6.480)
- Median duration of complete or partial response (until first documented disease progression) was 214 days (mean: 184.100; standard error: 19.595).
- Median duration of stable disease (time from informed consent to first documented disease progression, CR, PR or death) was 80 days (mean: 102.946; standard error: 9.501).
- Time to documented disease progression was 219 days (mean: 260.182; standard error: 22.954).
- Time to treatment failure (time from study inclusion to disease progression, death or early discontinuation for any reason) was 133.5 days (mean: 135.579; standard error: 13.737).
- Progression-free survival was defined as time from informed consent to disease progression or death. Median progression-free survival was 203 days (mean: 223.501; standard error: 21.227).
- Overall survival (time from informed consent until death) was 321 days (mean: 264.190; standard error: 15.130).

Additionally, some of the secondary variables were analyzed excluding those patients who had received another treatment before disease progression, with similar results: time to complete or partial response was 192 days (mean: 171.971; standard error: 23.390); duration of stable disease was 91 days (mean: 110.379; standard error: 11.708); time to disease progression was 203 days (mean: 241.287; standard error: 25.707); and progression-free survival was 190 days (mean: 208.773; standard error: 23.182).

All patients experienced at least one adverse event during the study. Of these patients, 94.7% had a drug-related adverse event, in the opinion of the investigator. The most frequently drug-related adverse effects reported were the following: Asthenia (71.1%), nausea and vomiting (55.3%, respectively), diarrhoea (47.4%) and anorexia (44.7%).

42.1% of the patients experienced at least one serious adverse event. Of these, 21.1% were considered drug-related events, in the opinion of the investigator. With regard to drug-related serious adverse events, the following were the most frequently reported: neutropenia (10.5%) and diarrhoea, vomiting and leukopenia (7.9%, respectively).

Twelve patients (36.1%) discontinued early because of an adverse event or toxicity.

18 deaths occurred during the study. 2 deaths occurred during the treatment period (patient number 403 – leukopenia, neutropenia, thrombocytopenia and renal failure; and patient number 501 – cardiac arrest), while 16 deaths occurred during the follow-up period, due to disease progression.

In general, toxicities experienced during the study were mild or moderate. Grade 4 hematologic toxicity was rarely observed: neutropenia was the most severe toxicity (present in 8.3% of all cycles and 21.1% of all patients).

Median time patients remain in the study before discontinuation was 296.5 days (standard deviation: 159.6) and drug exposure time was 126 days (IQR: 77-154).

Conclusions:

- 39.5% of the patients had a best study response of complete or partial response (similar response rates as in previous studies with the same drug for other types of cancer).
- Progression-free survival was approximately 6 months (similar result as in other studies).
- Overall survival was 321 days.
- The most frequently reported adverse events were asthenia, nausea, vomiting, diarrhoea and anorexia.
- 21.1% of the patients had a drug-related serious adverse event. Some drug-related serious adverse events were neutropenia (4 patients) and diarrhoea, vomiting and leukopenia (3 patients, respectively).
- 18 deaths occurred during the study. Two of these deaths occurred during the treatment period, while the remaining 16 deaths happened during the follow-up period.